Single Nucleotide Polymorphisms: An Approach to Personalized Medicine for African Americans with and without Type 2 Diabetes Mellitus

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Abstract Over 27 million people in the U.S. have type 2 diabetes mellitus, with a disproportionate number being African American. There is abundant evidence of environmental and genetic influence, with several single nucleotide polymorphisms reaching genome-wide significance. The work was a pilot study to begin to determine whether type 2 diabetes mellitus can be improved in society through personalized medicine, by approaching individual patients from the standpoint of their unique at-risk or protective genes in addition to lifestyle and family history. Twenty-seven patients volunteered to answer questions on family history of type 2 diabetes mellitus and had their body mass index, glucose, glycosylated hemoglobin, and insulin levels determined. They also had DNA extracted with single nucleotide polymorphisms determined by Affymetrix precision medicine research array. Fourteen single nucleotide polymorphisms relating to T2DM were found in the microarray used in this study. Number of at-risk single nucleotide polymorphisms varied for participants and 3 had the protective single nucleotide polymorphisms. While all participants had at-risk single nucleotide polymorphisms, some individuals with a body mass index in the obese range or with family history of the disease were found to have a greater number of single nucleotide polymorphisms that place them at risk for type 2 diabetes mellitus. This study shows how combined knowledge of patient single nucleotide polymorphisms, family history, and lab parameters may provide information for developing a personalized medicine plan.

Keywords African American Health, Type 2 Diabetes Mellitus, Personalized Medicine, Single Nucleotide Polymorphisms

diabetes, over 90% of which have type 2 diabetes mellitus (T2DM) [1]. Between 2013 and 2015, it was found that African Americans had a higher age-adjusted incidence at 12.7% compared to Caucasians with 7.4% of the population [(2). There is also an enormous economic cost associated with T2DM, with total expenditure rising from \$174 billion to \$245 billion from 2007 to 2012[(3].

In 2015, President Barack Obama announced the Precision Medicine Initiative® in his State of the Union Address [4]. Precision medicine aims to reduce disease and tailor treatment by considering individual variations in lifestyle, genes, and environment. This initiative proposes to generate evidence-based practice needed to translate the notion of precision medicine into clinical practice, with the goal of focusing on individualized treatments. This is important since some current treatments are not successful for everyone suffering from a disease since individuals vary based on these factors.

In order to help the high number of African Americans who may have risk-factors for diabetes or who have already been diagnosed with the disease, precision medicine could potentially benefit in prevention of treatment. With that in mind, human genome studies have identified several single nucleotide polymorphisms (SNPs) that are significantly associated with patients with T2DM. For example, rs7560163 reached genome-wide significance in several studies [5,6]. Many other SNPs have been correlated with increases in T2DM specifically in African American individuals, such as rs2021785, rs6769511, and rs864745 [7-9]. Furthermore, several SNPs have been found to correlate with an increase of T2DM in AA individuals in more than one published study. For example, SNP rs7903146 was significantly correlated with T2DM in a genome wide association study (GWAS) by Long et al. and was found to correlate with an increased risk by McCormack et al. [5,8]. Alternatively, rs1421085 actually offers protection from T2DM for African American individuals with the C allele [10]). For prevention and treatments purposes, we now have the

1. Introduction

More than 30 million people in the U.S. suffer from

knowledge to move forward and use these findings to help individuals understand how their unique genetic variations may make them more predisposed to or protected from T2DM, or possibly a combination of each.

Patients may benefit from knowing the specific SNP alleles relating to T2DM that are represented in their genome. This knowledge can subsequently allow a personalized plan to be better developed even before their glucose, hemoglobin A1c (HbA1c), and insulin levels begin to falter. This could help prevent many cases of T2DM from occurring. In cases where patients are already considered as having “pre-diabetes”, a plan can be better designed to prevent them from developing T2DM. In this study, African American participants were screened in order to determine family history of diabetes, to determine laboratory values that correlate with diagnosis of T2DM, and their DNA was extracted in order to determine which participants carry genes that are at-risk or protective toward the disease. This information was used to determine whether there is correlation between individual SNPs, family history, and lab values and to potentially begin to focus on personalized medicine plans for T2DM. To our knowledge, a study that includes presenting SNPs of individuals in comparison to lab values relevant to diabetes as well as their family history has not been presented before, especially in reference to conversations about personalized medicine.

2. Materials and Methods

African American patients visiting the Community Care Center in Winston-Salem, NC were asked to volunteer. After consent forms were signed, participants were briefly interviewed to determine whether or not they had ever been diagnosed with T2DM and whether they have a family history of diabetes. Participants without T2DM were assigned a number between 1a and 1l while those with T2DM were assigned a number between 2a and 2l, and those with “pre-diabetes” were assigned a number between 3a and 3c. Age, sex, race, and body mass index (BMI) were also recorded. Non-fasting glucose levels were measured using TRUE METRIX PRO glucose meter by NIPRO Diagnostics [11]. HbA1c levels were measured using A1C NOW kit by PTS Diagnostics [12]. Insulin levels were determined using the Crystal Chem Insulin ELISA Kit [13]. DNA was extracted using Qiagen DNeasy Blood and Tissue Kit and then sent for Affymetrix Precision Medicine Research Array (PMRA) to AKESOGene [14-16]. The presence of SNPs relating to T2DM were determined for each participant.

3. Results

Each participant self-described himself/herself as

African American. Table 1 indicates results for each participant including age, sex, BMI, HbA1c, and insulin as well as how the participant described any family history of diabetes. Study participants 1a-1l described themselves as not having T2DM, 2a-2l as having T2DM, and 3a-3c as having pre-diabetes. Participants describing themselves as not having T2DM had an age range from 24 to 64 years, with 6 females and 6 males, BMI average of 33.0, glucose average of 98.1 mg/dl, HbA1c average of 5.8%, and insulin level average of 9.2 mU/l. Of 12 participants, 7 reported having any family history of diabetes. For those classified as having T2DM there were 6 females and 6 males, age range between 40 and 60 years, with averages as follows: BMI of 33.6, glucose of 127 mg/dl, HbA1c of 6.8%, and insulin level of 10.5 mU/l. All except one reported some history of diabetes. Of the 3 self-reported patients with pre-diabetes, all were female ages 27, 61, and 64, with one reporting a history of T2DM. Average values were as follows: glucose of 109 mg/dl, HbA1c of 6.0%, BMI of 38.7, and insulin level of 17.3 mU/l.

Table 2 indicates SNPs that were found in this study relating to T2DM along with the gene and/or specific alleles correlating with the disease as evidenced through previous genome studies. It also indicates whether this SNP has been previously shown to provide protection or increased risk of T2DM. Also included are the participants from this study that had the particular SNP allele, whether major or minor, and homozygous or heterozygous. Participants 1d, 1f, and 3a were found to be heterozygous for the protective C allele for rs1421085.

Table 3 indicates which major and minor alleles each participant had in their genome. Participant 1d not only had the protective allele, but was also homozygous for the major allele for 7 at-risk SNPs and heterozygous for 4 others. Similarly, participant 1f was homozygous for major alleles for three at-risk SNPs, heterozygous for 7 others, and homozygous for one minor allele.

Of the SNPs that have been shown to increase the risk for T2DM in African Americans or all populations, all participants in the study were homozygous for several of these SNPs and almost all were heterozygous for more than one. All participants in the study were homozygous for the major allele of the SNP found to have genome-wide significance for risk of T2DM, rs7560163, except for 1e and 2h, both of whom were heterozygous for the SNP. Overall those participants who did not have diabetes were homozygous for 60 of the major alleles while those with the disease had 64. The group without diabetes were heterozygous for 41 major alleles while those with the disease had 32.

The Affymetrix Precision Medicine Research Array includes about 903,000 different SNPs [15]. Therefore, of the various SNPs previously shown to relate to T2DM, not all were found in this array and so what is represented in the data of this study are the SNPs that were among those included. For example, rs231362 was not found in this PMRA panel even though it was found in a study by Long

et al. to be associated with a higher risk of T2DM when individuals carry the GA alleles for the KCNQ1 gene at this location [10]. None of the participants that volunteered for this study had the A/G alleles of the rs864745 or the

T/C alleles of the rs4689388 SNP. Alternatively, all participants were homozygous for the C allele for the rs1801282 SNP for the PPARG gene, except for participants 1g and 1i who were heterozygous.

Table 1. Age, sex, BMI, glucose, HbA1c, insulin, and any family history from all 27 African American patient volunteers

Participant	Age	Sex	BMI	Glucose(mg/dl)	A1C (%)	Insulin (mU/l)	Family History (family member, if offered)*
1a	56	M	31	81	5.4	4.2	Yes, Maternal Aunt
1b	24	M	22.2	117	5.4	3.9	No
1c	35	F	66.8	90	5.7	4.8	Yes
1d	43	F	31.2	99	5.9	4.8	No
1e	46	F	42.5	91	4.9	4.1	No
1f	37	M	28.6	106	7.3	3.1	Yes
1g	44	F	31.2	92	5.5	7.7	No
1h	49	F	31.8	117	6	3.5	Mother; Grandfather (Type 1)
1i	61	M	34.7	109	6.5	8.1	Yes, 3 Brothers, 2 Sisters
1j	64	M	27.4	95	5.8	6.9	No
1k	53	M	24.8	89	6.1	6.1	Yes, Mother
1l	26	F	23.3	91	4.9	9.12	Yes, Father
2a	55	M	42	105	6.3	27.5	Yes, Mother
2b	55	M	29.3	176	8.1	6.93	Yes, Parents, 3 Brothers, 1 Sister
2c	57	M	34.2	137	6.1	3.5	Yes
2d	59	M	25.8	101	6.3	3.5	Yes, Grandparents
2e	61	F	38.2	102	6.8	4.1	Yes, Mother
2f	58	M	33.8	189	8.8	15.8	Yes, Mother, Maternal Grandfather
2g	61	M	40.1	165	7.1	29.9	Yes, Thinks Brothers Have Diabetes
2h	60	F	30.1	98	5.8	4.6	Yes
2i	54	F	31.7	91	6.2	5.0	Yes
2j	58	F	28.5	81	6	6.9	No
2k	40	F	38.8	97	5.6	13.8	Yes, Grandmother
2l	59	F	30.6	182	8.2	4.9	Yes, Mom and Grandmother
3a	27	F	54.3	106	5.4	41.5	Yes, Grandmother
3b	61	F	38	103	6.7	4.6	No
3c	64	F	23.8	118	5.8	5.8	No

*yes responses are type 2 unless otherwise indicated participants in group 1=no diabetes, 2=diabetes, 3=prediabetes

Table 2. Participants with protective or at-risk allele for SNPs relating to diabetes.

SNP	Gene/Allele(s)*	Impact on Diabetes	HM Participants, Major Allele	HT Participants	HM Participants, Minor Allele
rs1421085	FTO: C	Protective ^{5,10}	none	1d, 1f, 3a	N/A
rs864745	JAZF1: A/G	AA and T2DM risk ⁹	None	None	None
rs2021785	PCSK2: C/T	AA and T2D risk ⁹	1d, 1e, 1g, 1h, 2a, 2b, 2c, 2f, 2h, 2i, 2l, 3b, 3c	1a, 1b, 1e, 1i, 1j, 1k, 2d, 2e, 2g, 2j, 2k, 3a	1c
rs6769511	IGF2BP2: C/T	AA and T2DM risk ⁸	1a, 1b, 1c, 1d, 1e, 1g, 1h, 1k, 2c, 2g, 2f, 2j, 2k, 2l, 3a, 3c	1f, 1j, 2b, 2d, 2e, 3b, 1j	None
rs4689388	WFS1/PPP2R2C : T/C	AA and T2DM risk ⁸	None	None	None
rs231362	KCNQ1: G/A	AA and T2DM risk ⁸	SNP not in PMRA panel		
rs2237892	KCNQ1: C/T	AA and T2DM risk ⁸	1a, 1b, 1c, 1d, 1g, 1i, 1k, 1l, 2b, 2c, 2d, 2e, 2g, 3b	1e, 1f, 1h, 1j, 2a, 2f, 2k, 3a	2h, 3c
rs2237897	KCNQ1: C/T	AA and T2DM risk ⁸	1c, 1d, 1f, 1g, 1h, 1k, 2a, 2b, 2c, 2d, 2e, 2h, 2i, 2j, 2l, 3a, 3b	1a, 1b, 1e, 1f, 1j, 1l, 2f, 2g, 3c	2h
rs7903146	1-TCF7L2: T/C 2-T if low HDL, obesity	1-AA and T2DM risk ⁸ 2-GWAS significance correlating AA and T2DM risk ¹⁸	1b, 2d, 2k	1a, 1d, 1g, 1l, 2b, 2g, 2i, 2j, 3a	1c, 1e, 1f, 1i, 1k, 2a, 2c, 2e, 2f, 2h, 2k, 3b, 3c
rs1801282	PPARG: C	AA in Europe and T2DM risk ¹⁸	All participants except 1g, 1i	CG=1g, 1i	N/A
rs4402960	IGF2PBP2:T	All racial groups in Europe ¹⁸	1c, 1e, 1g, 1k, 1l, 2c, 2j, 2k, 2l, 3c	TG=1a, 1d, 1f, 1h, 2b, 2e, 2f, 2g, 2h, 2i, 3a, 3b	N/A
rs7560163	C/G	GWAS significance correlating AA and T2DM risk ^{5,6}	All except 1e, 2h	1e, 2h	None
rs7542900	C/T	AA and T2DM risk ⁶	1d, 1j, 1l, 2b, 2f, 2g, 2h, 3a	1c, 1e, 1f, 1g, 1h, 1i, 2c, 2d, 2g, 2i, 2k, 3b, 3c	1a, 1b, 2a, 2e, 2j, 2l
rs7107217	C/A	AA and T2DM risk ⁶	1c, 1g, 2a, 2e, 2k, 3a, 3b, 3c	1a, 1d, 1f, 1h, 1i, 1j, 1k, 1l, 2b, 2f, 2i, 2j, 2l	1b, 1e, 2c, 2d, 2g, 2h

AA= African Americans, HM=homozygous, HT=heterozygous, *major/minor alleles; participants in group 1=no diabetes, 2=diabetes, 3=prediabetes

Table 3. SNPs with major and minor alleles for each participant.

No Diabetes	SNPs	Diabetes	SNPs
1a	Major, HM: rs6769511, rs2237892, rs1801282, rs7560163, HT: rs2021785, rs2237897, rs7903146, rs4402960, rs7107217 Minor: rs7542900	2a	Major, HM: rs2021785, rs2237897, rs1801282, rs7560163, rs7107217 HT: rs2237892, rs7542900 Minor: rs7542900
1b	Major, HM: rs6769511, rs2237892, rs7903146, rs1801282, rs7560163 HT: rs2021785, rs2237897 Minor: rs7542900, rs7107217	2b	Major, HM: rs2021785, rs2237892, rs2237897, rs1801282, rs7560163, rs7542900 HT: rs6768511, rs7903146, rs4402960, rs7107217 Minor: None
1c	Major, HM: rs6769511, rs2237892, rs2237897, rs1801282, rs7560163, rs4402960, rs7107217 HT: rs7542900 Minor: rs2021785, rs7903146	2c	Major, HM: rs2021785, rs6769511, rs2237892, rs2237897, rs1801282, rs7560163, rs4402960 HT: rs7542900 Minor: rs7107217
1d	Major, HM: rs2021785, rs6769511, rs2237892, rs2237897, rs1801282, rs7560163, rs7542900 HT: rs1421085, rs7903146, rs4402960, rs7107217 Minor: None	2d	Major, HM: rs2237892, rs2237897, rs7903146, rs1801282, rs7560163 HT: rs2021785, rs6768511, rs7542900 Minor: rs7107217
1e	Major, HM: rs6769511, rs2237897, rs1801282, rs4402960 HT: rs2021785, rs2237892, rs7560163 Minor: rs7903146, rs7107217	2e	Major, HM: rs2237892, rs2237897, rs1801282, rs7560163, rs7107217 HT: rs2021785, rs6768511, rs4402960 Minor: rs7542900
1f	Major, HM: rs2237897, rs1801282, rs7560163 HT: rs1421085, rs6768511, rs6768511, rs2237892, rs4402960, rs7542900, rs7107217 Minor: rs7903146	2f	Major, HM: rs2021785, rs6769511, rs2237897, rs1801282, rs7542900 HT: rs2237892, rs4402960, rs7107217 Minor: None

1g	Major,HM:rs2021785, rs6769511, rs2237892, rs2237897,rs7560163,rs4402960,rs7107217 HT: rs7903146, rs1801282,rs7542900 Minor:None	2g	Major,HM: rs6769511,rs2237892, rs2237897, rs1801282,rs7560163,rs7542900 HT:rs2021785, rs7903146, rs4402960, rs7542900 Minor: rs7107217
1h	Major,HM:rs2021785, rs6769511, rs2237897,rs1801282,rs7560163 HT: rs2237892,rs4402960,rs7542900, rs7107217 Minor:None	2h	Major,HM:rs2021785,rs2237897,rs1801282, rs7542900 HT: rs7560163,rs4402960 Minor: rs2237892,rs2237897, rs7107217
1i	Major,HM: rs2237892,rs7560163 HT:rs2021785,rs1801282,rs7542900, rs7107217 Minor: rs7903146	2i	Major,HM:rs2021785,rs2237897, rs1801282,rs7560163 HT: rs7903146,rs4402960,rs7542900, rs7107217 Minor:None
1j	Major,HM: rs2237897,rs1801282,rs7560163, rs7542900 HT:rs2021785, rs6768511, rs2237892, rs7107217 Minor:None	2j	Major,HM: rs6769511 rs2237897, rs1801282,rs7560163,rs4402960 HT:rs2021785, rs7903146, rs7107217 Minor:rs7542900
1k	Major,HM: rs6769511, rs2237892, rs2237897, rs1801282,rs7560163,rs4402960 HT:rs2021785, rs7107217 Minor: rs7903146	2k	Major,HM: rs6769511,rs7903146, rs1801282,rs7560163,rs4402960, rs7107217 HT:rs2021785, rs2237892, rs7542900 Minor:None
1l	Major,HM: rs2237892, rs2237897, rs1801282,rs7560163,rs4402960,rs7542900 HT: rs7903146,rs7107217 Minor: rs7903146	2l	Major,HM:rs2021785,rs6769511, rs2237897, rs1801282,rs7560163, rs4402960 HT: rs7107217 Minor:rs7542900
		Pre-Diabetes	
		3a	Major,HM: rs6769511,rs7542900,rs2237897, rs1801282,rs7560163,rs7107217,rs7542900, rs7107217 HT:rs2021785, rs2237892 rs7903146,rs4402960,rs1421085 Minor:None
		3b	Major,HM:rs2021785,rs2237892, rs2237897, rs1801282,rs7560163, rs7107217 HT: rs6768511,rs4402960,rs7542900 Minor:
		3c	Major,HM:rs2021785,rs6769511, rs2237897,rs1801282,rs7560163, rs4402960, rs7107217 HT: rs7542900 Minor: rs2237892

HM=homozygous, HT=heterozygous, major/minor alleles; participants in group 1=no diabetes, 2=diabetes, 3=prediabetes

3. Discussion

What can be inferred from the information in the tables includes potential benefits of precision medicine for each study participant. The participants with the protective C allele of rs1421085 indeed reported as either not having diabetes or having pre-diabetes; however, the HbA1c of 1d was 5.9 and that of 1f was 7.3. This suggests that these patients may benefit some personalized care from the healthcare provider to prevent T2DM. In addition, participant 3a who self-reported as having pre-diabetes has a BMI of 54.3, HbA1c of 5.4, and a grandmother with T2DM. She had the greatest number of at-risk SNPs found in this study at twelve, along with the one SNP associated with protection against the disease. A physician might share this information with her and recommend decreasing her BMI along with a healthier diet in order to decrease the risk of her further developing T2DM. The provider could help develop a personalized plan to reach these goals as a

vital component of health-related counselling after speaking with her about her genetic and family-history risk factors. Thus, this personalized counselling model can be extended to each participant in this study with the aim of optimizing the patient's treatment outcome.

In another example, individual 1a is a 56-year-old male without diabetes, but with an elevated BMI and a maternal aunt with T2DM despite having normal glucose and HbA1c values. Individual 1a does have a number of at-risk alleles for T2DM, including being homozygous for major at-risk alleles for rs6769511, rs2237892, rs1801282, rs7560163 and heterozygous for rs2021785, rs2237897, rs7903146, rs4402960, and rs7107217. In addition, according to Yan et al. if an obese patient has low HDL with the T allele at rs7903146, the patient is at increased risk for T2DM [17]. Participant 1a is indeed obese according to his BMI of 31, but we do not have the HDL value. Making this individual aware of this information may allow him to realize the importance of working to

decrease the BMI through healthier eating and increased exercise since these SNPs make him more at-risk for T2DM. Practitioners can also determine a personalized plan for this participant and set healthier goals accordingly. Similarly, patient 1f has the greatest number of at-risk SNPs of all the participants without diabetes in the study, suggesting that a personalized plan to prevent the onset of T2DM could be beneficial, perhaps by focusing on reducing the HbA1c and reducing the BMI. The reported HbA1c of 7.3 for participant 1f is great enough to be considered having diabetes and it could be that this was a new, as of yet, undiscovered case.

The participant in this study with diabetes having the most at-risk SNP alleles was 2g with eleven. For six of these she was homozygous for the major allele, heterozygous for 4 of the major alleles, and she had one minor allele. This participant had a BMI of 40.1, HbA1c of 7.1, and believes she has brothers with the disease. If a practitioner shared the information of her risk factors for T2DM, this may allow her to better understand that she will need to stick with a developed plan to reduce the BMI and HbA1c values. It would be more advantageous to identify these risk factors well before the patient's HbA1c increases and develops symptoms of T2DM. Perhaps many more patients can prevent the onset by knowing their genetic risk factors early in life.

4. Conclusions

To our knowledge, studies comparing patient SNPs with lab values and family history has not been done before. This study indicates how knowledge of individual parameters such as BMI, glucose, HbA1c, and family history as well as specific protective and high-risk SNPs may be important in the development of a plan for personalized medicine from practitioners. Patients who have family history of T2DM or who have prediabetes can use this collective information to improve their health status through necessary nutritional adjustments and increased physical exercise under the care of a practitioner. Patients who have already been diagnosed with T2DM, if made aware of the complex relationship between their unique family history, present blood values and BMI, and specific genes that make them more at-risk can better understand their personal relationship with the disease in order to better control it. Since African Americans have a greater number of cases of diabetes than Caucasians, increasing the use of personalized medicine for treatment of this disease could be of great benefit, personally and on an economic level.

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Disclosures

None

Abbreviations: type 2 diabetes mellitus (T2DM), single nucleotide polymorphism (SNP), body mass index (BMI), African Americans (AA)

Human Genes: JAZF1= juxtaposed with another zinc finger gene 1, PCSK2= proprotein convertase subtilisin/kexin type2, IGF2BP2= insulin like growth factor 2 mRNA binding protein 2, WFS1= wolframin ER transmembrane glycoprotein, PPP2R2C= protein phosphatase 2 regulatory subunit Bgamma, KCNQ1= potassium voltage-gated channel subfamily Q member 1, TCF7L2= transcription factor 7 like 2, PPARG= peroxisome proliferator activated receptor gamma.

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